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=> d his

     (FILE 'HOME' ENTERED AT 09:41:38 ON 30 MAY 2003)

     FILE 'CAPLUS' ENTERED AT 09:41:44 ON 30 MAY 2003
L1           29 S TERFENADIN?(L)(NONCRYSTAL? OR AMORPHO? OR POWDER? OR SPRAY? O
L2           15 S L1 AND SPRAY?
L3           12 S L2 AND PY<1999
L4            5 S L1(L)AMORPH?

=> s l1 and (terfenadin?(5a)(metaboli? or acid))
          1029 TERFENADIN?
        810462 METABOLI?
       3644542 ACID
           110 TERFENADIN?(5A)(METABOLI? OR ACID)
L5           3 L1 AND (TERFENADIN?(5A)(METABOLI? OR ACID))

=> d bib abs 1-3

L5   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2003 ACS
AN   2000:786497  CAPLUS
DN   134:357438
TI   Application of microcalorimetry in the pharmaceutical technology. Part I.
     Characterization of solid pharmaceuticals by heats of solution and
     crystallization measurement
AU   Yonemochi, Etsuo; Yoshihashi, Yasuo; Terada, Katsuhide
CS   School of Pharmaceutical Sciences, Toho University, Funabashi, Chiba,
     274-8510, Japan
SO   Pharm Tech Japan (1999), 15(5), 723-726, 729-731
     CODEN: PTJAE9; ISSN: 0910-4739
PB   Yakugyo Jihosha
DT   Journal; General Review
LA   Japanese
AB   A review with 9 refs. This review describes an approach of
     microcalorimetry to the characterization of pharmaceutical solids. The
     heats of soln. of indomethacin polymorphs were measured in a
     microcalorimeter. The heat of transition from .alpha.- to .gamma.-form
     was precisely obtained. The disordered levels of amorphous
     clarithromycin, ursodeoxychalic acid and terfenadine
     obtained by grinding and spray drying were evaluated by using
     the heat of soln. measurement. The heat of soln. of amorphous
     samples was greater than that of cryst. sample. A good correlation was
     obsd. between crystallinity and heat of soln. for the partially
     amorphous samples. The relationship between crystallinity and
     logarithm of dissoln. rate was derived, and a linear correlation was
     obtained. The heat of crystn. was studied for low degree of
     amorphous content powders. The microcalorimetry showed
     the ability to detect the existence of amorphous material even
     for mixts. which contain less than 1% wt./wt. The deconvolution theory
     was applied to the microcalorimetric data for kinetic study of dissoln.
     rate. The dissoln. profile was calcd. from the calorimetric traces for
     the heat of diln. and the heat of soln. by a numerical deconvolution. The
     disintegration and dissoln. mechanisms of tablet were estd. from the
     dissoln. rate profile obtained by the calorimetric method.

L5   ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2003 ACS
AN   1999:672611  CAPLUS
DN   131:291312
TI   Compositions containing terfenadine metabolites in
     combination with leukotriene inhibitors
IN   Rubin, Paul D.
PA   Sepracor Inc., USA
```

SO PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9952554	A1	19991021	WO 1999-US8077	19990413
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6194431	B1	20010227	US 1998-59570	19980414
CA 2328074	AA	19991021	CA 1999-2328074	19990413
AU 9936409	A1	19991101	AU 1999-36409	19990413
BR 9909641	A	20001219	BR 1999-9641	19990413
EP 1071463	A1	20010131	EP 1999-918515	19990413
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2002511426	T2	20020416	JP 2000-543164	19990413
NO 2000005147	A	20001107	NO 2000-5147	20001013
US 6509353	B1	20030121	US 2000-722395	20001128
US 2003083343	A1	20030501	US 2002-314269	20021206
PRAI US 1998-59570	A	19980414		
WO 1999-US8077	W	19990413		
US 2000-722395	A3	20001128		

AB Methods and pharmaceutical compns. employing a **terfenadine metabolite** and a leukotriene inhibitor for the treatment or prevention of inflammation or allergic disorders, such as asthma, or symptoms are described. Me 4-[1-oxo-4-(4-hydroxydiphenylmethyl-1-piperidinyl)butyl]-.alpha.,.alpha.-dimethylbenzeneacetate (I) was prepd. by the reaction of 4-(.alpha.-hydroxy-.alpha.-phenylbenzyl)piperidine with Me p-(4-chloro-1-oxobutyl)-.alpha.,.alpha.-dimethylbenzeneacetate in Me iso-Bu ketone in the presence of KHCO3 and KI. I was reduced with the chiral agent, (+)-.beta.-chlorodiisopinocamphenylborane to give Me (R)-4-[1-hydroxy-4-(4-hydroxydiphenylmethyl-1-piperidinyl)butyl]-.alpha.,.alpha.-dimethylbenzeneacetate which was hydrolyzed by KOH in EtOH to afford (R)-(+)-fexofenadine.

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS
AN 1995:338851 CAPLUS
DN 122:114785
TI Study of the salts with organic hydroxy acids of the **terfenadine** .beta.-cyclodextrin inclusion complex in solution by ion-**spray** mass spectrometry
AU Selva, Antonio; Redenti, Enrico; Pasini, Massimo; Ventura, Paolo; Casetta, Bruno
CS Cent. Studio Sostanze Organische Naturali, Dip. Chim., Milan, I-20131, Italy
SO Journal of Mass Spectrometry (1995), 30(1), 219-20
CODEN: JMSPFJ; ISSN: 1076-5174
PB Wiley
DT Journal
LA English
AB A **terfenadine** (TFN)-.beta.-cyclodextrin (.beta.-CD)-hydroxycarboxylic acid multicomponent system was studied by ion-

spray mass spectrometry. Protonated or cationated 1:1:1 TFN-.beta.-CD-citric acid adducts were unambiguously detected in the gas phase.

```
=> s terfenadin?(l)(noncrystal? or amorpho? or powder? or spray? or freez?)
          1029 TERFENADIN?
          2928 NONCRYSTAL?
        220745 AMORPHO?
        519091 POWDER?
        213078 SPRAY?
         95303 FREEZ?
L1          29 TERFENADIN?(L)(NONCRYSTAL? OR AMORPHO? OR POWDER? OR SPRAY? OR
               FREEZ?)
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=> s l13 and py<1999
      18916304 PY<1999
L14          10 L13 AND PY<1999

=> d bib 1-10

L14  ANSWER 1 OF 10  CAPLUS  COPYRIGHT 2003 ACS
AN   1998:618722  CAPLUS
DN   129:244200
TI   Process for production of 4-(4-(4-hydroxydiphenylmethyl-1-piperidinyl)-1-
     hydroxybutyl)-.alpha.,.alpha.-dimethylphenylacetic acid and phosphorylated
     derivatives
IN   Meiwes, Johannes; Worm, Manfred
PA   Hoechst Marion Roussel Deutschland G.m.b.H., Germany
SO   Eur. Pat. Appl., 13 pp.
     CODEN: EPXXDW
DT   Patent
LA   German
FAN.CNT 1
     PATENT NO.         KIND  DATE           APPLICATION NO.   DATE
     ---------------    ----  --------       ---------------   --------
PI   EP 864653          A1    19980916       EP 1998-103599    19980302 <--
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
            IE, SI, LT, LV, FI, RO
     DE 19709898        A1    19980924       DE 1997-19709898  19970311 <--
     DE 19751498        A1    19990527       DE 1997-19751498  19971121
     CA 2231588         AA    19980911       CA 1998-2231588   19980309 <--
     US 5990127         A     19991123       US 1998-36673     19980309
     JP 10259191        A2    19980929       JP 1998-57634     19980310 <--
     BR 9803289         A     20000502       BR 1998-3289      19980310
PRAI DE 1997-19709898   A     19970311
     DE 1997-19751498   A     19971121
RE.CNT  5      THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14  ANSWER 2 OF 10  CAPLUS  COPYRIGHT 2003 ACS
AN   1998:283151  CAPLUS
DN   128:321543
TI   An efficient and facile synthesis of racemic and optically active
     fexofenadine
AU   Fang, Qun K.; Senanayake, Chris H.; Wilkinson, H. Scott; Wald, Stephen A.;
     Li, Hui
CS   Chem. Res. Dev., Sepracor Inc., Marlborough, MA, 01752, USA
SO   Tetrahedron Letters (1998), 39(18), 2701-2704
     CODEN: TELEAY; ISSN: 0040-4039
PB   Elsevier Science Ltd.
DT   Journal
LA   English
RE.CNT  20     THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
               ALL CITATIONS AVAILABLE IN THE RE FORMAT

L14  ANSWER 3 OF 10  CAPLUS  COPYRIGHT 2003 ACS
AN   1997:503139  CAPLUS
DN   127:135728
TI   Process for production of piperidine derivatives
IN   D'Ambra, Thomas E.; Pilling, Garry M.
PA   Albany Molecular Research, Inc., USA
SO   PCT Int. Appl., 93 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
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	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9723213	A1	19970703	WO 1996-US20189	19961219	<--
	W: AU, BR, CA, HU, JP, KR, MX, NO, NZ, RU, UA, UG					
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
	US 6153754	A	20001128	US 1995-576068	19951221	
	CA 2240927	AA	19970703	CA 1996-2240927	19961219	<--
	AU 9713371	A1	19970717	AU 1997-13371	19961219	<--
	AU 723231	B2	20000824			
	EP 868182	A1	19981007	EP 1996-944868	19961219	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
	BR 9612216	A	19991228	BR 1996-12216	19961219	
	JP 2000502348	T2	20000229	JP 1997-523790	19961219	
	NZ 326085	A	20010427	NZ 1996-326085	19961219	
	NO 9802770	A	19980616	NO 1998-2770	19980616	<--
	US 6444824	B1	20020903	US 2000-634983	20000809	
	US 6458958	B1	20021001	US 2000-637127	20000809	
	US 2003028029	A1	20030206	US 2002-212829	20020805	
PRAI	US 1995-576068	A	19951221			
	WO 1996-US20189	W	19961219			
	US 2000-634983	A1	20000809			

OS MARPAT 127:135728

L14 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 1997:502862 CAPLUS
DN 127:121642
TI Preparation of 4-(4-piperidino-1-hydroxybutyl)-.alpha.,.alpha.-dimethylphenylacetates and analogs as antiallergics, antihistaminics, and bronchodilators
IN D'ambra, Thomas E.; Pilling, Garry M.
PA Albany Molecular Research, Inc., USA
SO PCT Int. Appl., 113 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9722344	A1	19970626	WO 1996-US20769	19961219	<--
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	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
	US 6201124	B1	20010313	US 1995-575344	19951221	
	CA 2240735	AA	19970626	CA 1996-2240735	19961219	<--
	AU 9713547	A1	19970714	AU 1997-13547	19961219	<--
	AU 723759	B2	20000907			
	EP 877733	A1	19981118	EP 1996-945097	19961219	<--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI					
	BR 9612099	A	19991228	BR 1996-12099	19961219	
	JP 2000502105	T2	20000222	JP 1997-523095	19961219	
	NZ 326228	A	20000228	NZ 1996-326228	19961219	
	NO 9802806	A	19980812	NO 1998-2806	19980618	<--
	US 6448406	B1	20020910	US 2000-634775	20000809	
	US 6452011	B1	20020917	US 2000-634169	20000809	
PRAI	US 1995-575344	A	19951221			
	WO 1996-US20769	W	19961219			

OS MARPAT 127:121642

L14 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 1997:30147 CAPLUS
DN 126:83906
TI Fexofenadine hydrochloride. Terfenadine carboxylate hydrochloride.

MDL-16455A. Allegra
AU Graul, A.; Castaner, J.
CS Prous Science Publishers, Barcelona, 08080, Spain
SO Drugs of the Future (**1996**), 21(10), 1017-1021
CODEN: DRFUD4; ISSN: 0377-8282
PB Prous
DT Journal; General Review
LA English

L14 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 1996:755841 CAPLUS
DN 126:74717
TI Synthesis of terfenadine carboxylate
AU Patel, Sunil; Waykole, Liladhar; Repic, Oljan; Chen, Kau-Ming
CS Sandoz Res. Inst., Sandoz Pharmaceutical Corp., East Hanover, NJ, 07936, USA
SO Synthetic Communications (**1996**), 26(24), 4699-4710
CODEN: SYNCAV; ISSN: 0039-7911
PB Dekker
DT Journal
LA English

L14 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 1995:871983 CAPLUS
DN 123:285787
TI Preparation of [(hydroxybenzhydryl)piperidinoalkanoyl]phenylalkanoates and analogs as antihistaminics
IN Krauss, Richard C.; Strom, Robert M.; Scortichini, Carey L.; Kruper, William J.; Wolf, Richard A.; Carr, Albert A.; Rudisill, Duane E.; Panzone, Gianbattista; Hay, David A.; Wu, Weishi W.
PA Merrell Dow Pharmaceuticals Inc., USA
SO PCT Int. Appl., 236 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9500480	A1	19950105	WO 1994-US5982	19940526	<--
	W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN					
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
	CA 2166059	AA	19950105	CA 1994-2166059	19940526	<--
	CA 2362337	AA	19950105	CA 1994-2362337	19940526	<--
	CA 2362339	AA	19950105	CA 1994-2362339	19940526	<--
	AU 9470466	A1	19950117	AU 1994-70466	19940526	<--
	AU 699559	B2	19981210			
	EP 705245	A1	19960410	EP 1994-919264	19940526	<--
	EP 705245	B1	20030102			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					
	CN 1128987	A	19960814	CN 1994-193031	19940526	<--
	HU 74092	A2	19961128	HU 1995-3705	19940526	<--
	JP 08512028	T2	19961217	JP 1994-502831	19940526	<--
	EP 1260504	A1	20021127	EP 2002-12626	19940526	
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE					
	AT 230395	E	20030115	AT 1994-919264	19940526	
	ZA 9404380	A	19950209	ZA 1994-4380	19940620	<--
	IL 110086	A1	20010913	IL 1994-110086	19940622	
	FI 9506248	A	19960219	FI 1995-6248	19951222	<--
	NO 9505255	A	19960226	NO 1995-5255	19951222	<--
	AU 9915458	A1	19990624	AU 1999-15458	19990208	

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     AU 734870          B2   20010621
     CN 1274711         A    20001129       CN 2000-101035   20000112
     NO 2002002129      A    19960226       NO 2002-2129     20020503 <--
PRAI US 1993-82693      A    19930625
     US 1993-144084     A    19931027
     US 1994-237466     A    19940511
     AU 1994-70466      A3   19940526
     CA 1994-2166059    A3   19940526
     EP 1994-919264     A3   19940526
     WO 1994-US5982     W    19940526
OS   MARPAT 123:285787

L14  ANSWER 8 OF 10  CAPLUS  COPYRIGHT 2003 ACS
AN   1995:478306  CAPLUS
DN   122:239548
TI   Regioselective preparation of terfenadine analogs.
IN   D. Ambra, Thomas E.
PA   Albany Molecular Research, Inc., USA
SO   PCT Int. Appl., 58 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 2
     PATENT NO.         KIND  DATE           APPLICATION NO.  DATE
     ---------------    ----  --------       ---------------  --------
PI   WO 9500482         A1    19950105       WO 1994-US6873   19940621 <--
         W:  AU, CA, FI, HU, JP, KR, NO, NZ
         RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
     JP 11236373        A2    19940621       JP 1998-269606   19940621 <--
     JP 3195297         B2    20010806
     CA 2181089         AA    19941225       CA 1994-2181089  19940621 <--
     CA 2147126         AA    19950105       CA 1994-2147126  19940621 <--
     CA 2254506         AA    19950105       CA 1994-2254506  19940621 <--
     AU 9471748         A1    19950117       AU 1994-71748    19940621 <--
     AU 670004          B2    19960627
     EP 703902          A1    19960403       EP 1994-920762   19940621 <--
     EP 703902          B1    19981216
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
     HU 73235           A2    19960729       HU 1995-3719     19940621 <--
     EP 723958          A1    19960731       EP 1996-200338   19940621 <--
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
     AT 174589          E     19990115       AT 1994-920762   19940621
     ES 2129130         T3    19990601       ES 1994-920762   19940621
     JP 3034047         B2    20000417       JP 1995-502981   19940621
     EP 1026147         A1    20000809       EP 2000-200419   19940621
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE
     JP 2001031650      A2    20010206       JP 2000-233271   19940621
     JP 2002212166      A2    20020731       JP 2001-350148   19940621
     US 5589487         A     19961231       US 1995-382425   19950202 <--
     US 5750703         A     19980512       US 1995-382649   19950202 <--
     US 5578610         A     19961126       US 1995-456273   19950531 <--
     US 5581011         A     19961203       US 1995-455991   19950531 <--
     NO 9505023         A     19951212       NO 1995-5023     19951212 <--
     FI 9506270         A     19951227       FI 1995-6270     19951227 <--
     AU 9658372         A1    19961121       AU 1996-58372    19960705 <--
     AU 699799          B2    19981217
     US 5663412         A     19970902       US 1996-700556   19960808 <--
     US 5994549         A     19991130       US 1997-994357   19971219
     AU 9917422         A1    19990429       AU 1999-17422    19990222
     AU 729549          B2    20010201
     NO 9904582         A     19951212       NO 1999-4582     19990921 <--
PRAI US 1993-83102      A     19930624
     CA 1994-2147126    A3    19940621
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	EP 1994-920762	A3	19940621
	EP 1996-200338	A3	19940621
	JP 1995-502981	A3	19940621
	JP 1998-269606	A3	19940621
	JP 2000-233271	A3	19940621
	WO 1994-US6873	W	19940621
	US 1995-382649	A3	19950202
	US 1995-455991	A1	19950531
	AU 1996-58372	A3	19960705

OS CASREACT 122:239548; MARPAT 122:239548

L14 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 1994:270048 CAPLUS
DN 120:270048
TI A Facile Synthesis of an Oxidation Product of Terfenadine
AU Kawai, Stephen H.; Hambalek, Robert J.; Just, George
CS Department of Chemistry, McGill University, Montreal, QC, H3A 2K6, Can.
SO Journal of Organic Chemistry (**1994**), 59(9), 2620-2
CODEN: JOCEAH; ISSN: 0022-3263
DT Journal
LA English
OS CASREACT 120:270048

L14 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2003 ACS
AN 1981:156758 CAPLUS
DN 94:156758
TI Piperidine derivatives with antihistamine action
IN Carr, Albert A.; Dolfini, Joseph E.; Wright, George J.
PA Richardson-Merrell Inc., USA
SO Ger. Offen., 39 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	DE 3007498	A1	19801023	DE 1980-3007498	19800228	<--
	DE 3007498	C2	19890907			
	US 4254129	A	19810303	US 1979-28813	19790410	<--
	CA 1123438	A1	19820511	CA 1980-344020	19800118	<--
	IL 59158	A1	19840430	IL 1980-59158	19800118	<--
	ZA 8000332	A	19810128	ZA 1980-332	19800121	<--
	AU 8055016	A1	19801016	AU 1980-55016	19800129	<--
	AU 531146	B2	19830811			
	NL 8000754	A	19801014	NL 1980-754	19800207	<--
	NL 190580	B	19931201			
	NL 190580	C	19940502			
	CH 643245	A	19840530	CH 1980-1741	19800305	<--
	AT 8001448	A	19840315	AT 1980-1448	19800317	<--
	AT 376208	B	19841025			
	ES 489934	A1	19810316	ES 1980-489934	19800326	<--
	DK 8001329	A	19801011	DK 1980-1329	19800327	<--
	DK 153709	B	19880822			
	DK 153709	C	19881227			
	GB 2048258	A	19801210	GB 1980-10997	19800402	<--
	GB 2048258	B2	19830330			
	SE 8002634	A	19801011	SE 1980-2634	19800408	<--
	SE 448726	B	19870316			
	SE 448726	C	19870625			
	BE 882703	A1	19800731	BE 1980-200161	19800409	<--
	NO 8001014	A	19801013	NO 1980-1014	19800409	<--
	NO 154521	B	19860630			
	NO 154521	C	19861008			

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     JP 55141469        A2    19801105        JP 1980-45771     19800409 <--
     JP 01032823        B4    19890710
     FR 2453854         A1    19801107        FR 1980-7992      19800409 <--
     FR 2453854         B1    19830624
     US 4285957         A     19810825        US 1980-196505    19801014 <--
PRAI US 1979-28813              19790410
     US 1979-28872              19790410


=> s l14 and (freez? or rotary? or spray?)
         95303 FREEZ?
         41435 ROTARY?
        213078 SPRAY?
L15          0 L14 AND (FREEZ? OR ROTARY? OR SPRAY?)

=> s l14 and evapor?
         76354 EVAPOR?
L16          0 L14 AND EVAPOR?

=> s l14 and precipit?
         87974 PRECIPIT?
L17          0 L14 AND PRECIPIT?
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=> s fexofenadine/cn
L1            1 FEXOFENADINE/CN

=> d

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS
RN   83799-24-0  REGISTRY
CN   Benzeneacetic acid, 4-[1-hydroxy-4-[4-(hydroxydiphenylmethyl)-1-
     piperidinyl]butyl]-.alpha.,.alpha.-dimethyl- (9CI)  (CA INDEX NAME)
OTHER NAMES:
CN   4-[4-[4-(Hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-
     .alpha.,.alpha.-dimethylphenylacetic acid
CN   Carboxyterfenadine
CN   Fexofenadine
CN   MDL 16455
CN   Terfenadine acid metabolite
CN   Terfenadine carboxylate
FS   3D CONCORD
DR   159389-12-5, 76815-58-2
MF   C32 H39 N O4
CI   COM
LC   STN Files:  ADISINSIGHT, ADISNEWS, ANABSTR, BIOBUSINESS, BIOSIS, CA,
       CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN, CSCHEM, DDFU, DIOGENES,
       DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE, IPA, MEDLINE, MRCK*, PROMT,
       RTECS*, SYNTHLINE, TOXCENTER, USAN, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
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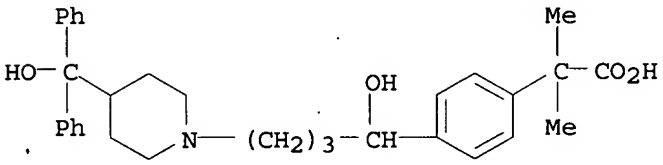


```
**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

             231 REFERENCES IN FILE CA (1957 TO DATE)
               8 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
             235 REFERENCES IN FILE CAPLUS (1957 TO DATE)


=> fil caplus
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     6.30       6.51

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FILE COVERS 1907 - 30 May 2003 VOL 138 ISS 23
FILE LAST UPDATED: 29 May 2003 (20030529/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

```
=> s l1
L2          235 L1

=> s l2(l)amorphous
         219932 AMORPHOUS
L3             1 L2(L)AMORPHOUS

=> d bib abs
```

L3 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
AN 2000:841983 CAPLUS
DN 134:21436
TI Preparation of amorphous fexofenadine hydrochloride using solvent method and spray or freezing drying techniques
IN Kumar, Naresh; Khanduri, Chandras Has; Sharma, Mukesh
PA Ranbaxy Laboratories Limited, India
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000071124	A1	20001130	WO 2000-IB708	20000525
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 1185266	A1	20020313	EP 2000-927651	20000525
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
PRAI	IN 1999-DE776	A	19990525		
	WO 2000-IB708	W	20000525		

AB This invention relates to the prepn. of amorphous form of fexofenadine hydrochloride (I) and to a compn. contg. it. The process for prepn. of amorphous form of I comprises (1) dissolving cryst. I in the lower alkanol solvent such as methanol, or in the ketone solvent such as acetone, or in the chlorinated solvent such as chloroform, and (2) recovering amorphous I by spray drying or freeze drying technique.

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
=> s terfenadine(l)metaboli?
          1026 TERFENADINE
        810462 METABOLI?
L1         167 TERFENADINE(L)METABOLI?

=> s l1 and py<1999
      18916304 PY<1999
L2          113 L1 AND PY<1999

=> s l2 and (fexofenadine(5a)hydrochloride)
           277 FEXOFENADINE
        126675 HYDROCHLORIDE
            60 FEXOFENADINE(5A)HYDROCHLORIDE
L3           3 L2 AND (FEXOFENADINE(5A)HYDROCHLORIDE)

=> d bib abs 1-3

L3   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2003 ACS
AN   1998:63366  CAPLUS
DN   128:188505
TI   Onset of action, efficacy, and safety of a single dose of
     fexofenadine hydrochloride for ragweed allergy using an
     environmental exposure unit
AU   Day, James Halliday; Briscoe, Maureen Phyllis; Welsh, April; Smith,
     Jeffrey Norman; Clark, Adrian; Ellis, Anne Kathleen; Mason, Jolene
CS   Div. Allergy, Kingston General Hospital, Kingston, ON, Can.
SO   Annals of Allergy, Asthma, & Immunology (1997), 79(6), 533-540
     CODEN: ALAIF6; ISSN: 1081-1206
PB   American College of Allergy, Asthma, & Immunology
DT   Journal
LA   English
AB   Fexofenadine hydrochloride is the active acid
     metabolite of terfenadine. Fexofenadine's anti-allergic
     properties require confirmation in a clin. setting. The purpose of this
     study was to characterize the time to onset of clin. important relief of
     symptoms of allergic rhinitis in subjects taking single doses of either 60
     mg or 120 mg fexofenadine HCl, or placebo, after exposure to ragweed
     pollen in a controlled environment. Other objectives were to assess the
     efficacy and safety of single doses of fexofenadine HCl. One hundred
     forty-six ragweed-sensitive subjects were primed in the off-season with
     ragweed pollen in the environmental exposure unit. One hundred thirty-six
     subjects who adequately responded to priming entered a single-dose placebo
     phase. Placebo-responders were disqualified from the study, leaving 99
     subjects with adequate symptoms to be randomized and given a single dose
     of either fexofenadine HCl 120 mg (33), 60 mg (33) or placebo (33), after
     60 min of allergen exposure. Exposure continued over five hours and
     subjects recorded symptoms every 20 min. This study was of a randomized,
     placebo-controlled, double-blind, parallel design. Median time to onset
     for relaxed criteria clin. important relief was 60 min for both
     fexofenadine treatment groups, and 100 min for placebo (P = .018). The
     proportion with relief was 82% at 60 mg, 85% at 120 mg, and 64% for
     placebo. Treated groups had redns. in symptom scores double that of
     placebo. Fexofenadine is safe and efficacious at single doses at 60 mg
     and 120 mg. Av. time on onset was 60 min using controlled pollen exposure
     in an environmental exposure unit.

L3   ANSWER 2 OF 3  CAPLUS  COPYRIGHT 2003 ACS
AN   1997:795273  CAPLUS
DN   128:97471
TI   Efficacy and safety of fexofenadine hydrochloride for
     treatment of seasonal allergic rhinitis
AU   Bernstein, David I.; Schoenwetter, William F.; Nathan, Robert A.; Storms,
```

William; Ahlbrandt, Robert; Mason, Jolene
CS Division of Immunology, University of Cincinnati College of Medicine, Cincinnati, OH, USA
SO Annals of Allergy, Asthma, & Immunology (**1997**), 79(5), 443-448
CODEN: ALAIF6; ISSN: 1081-1206
PB American College of Allergy, Asthma, & Immunology
DT Journal
LA English
AB Fexofenadine-HCl, the carboxylic acid **metabolite** of **terfenadine**, is a 2nd-generation antihistamine that is nonsedating and does not cause electrocardiog. effects. The clin. efficacy and safety of fexofenadine-HCl in the treatment of ragweed seasonal allergic rhinitis were studied, and the dose-response relationships at dosages of 60, 120, and 240 mg twice daily were characterized. Fexofenadine-HCl at each dosage provided significant improvement in total symptom score and in all individual nasal symptoms compared with placebo. The frequency of adverse events was similar among fexofenadine-HCl- and placebo-treated groups, with no dose-related trends. No sedative effects or electrocardiog. abnormalities, including prolongations in QTc, were detected. Thus, fexofenadine-HCl is both effective and safe for the treatment of ragweed seasonal allergic rhinitis. Because there was no addnl. efficacy at higher dosages, 60 mg twice daily appears to be the optimal therapeutic dosage for these patients.

L3 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2003 ACS
AN 1997:641645 CAPLUS
DN 127:322699
TI Effect of food on the bioavailability of **fexofenadine hydrochloride** (MDL 16 455A)
AU Stoltz, Maxine; Arumugham, Thangam; Lippert, Christina; Yu, Dale; Bhargava, Vijay; Eller, Mark; Weir, Scott
CS Departments Pharmacokinetics and Statistics, Hoechst Marion Roussel, Inc., Kansas City, MO, 64134-0627, USA
SO Biopharmaceutics & Drug Disposition (**1997**), 18(7), 645-648
CODEN: BDDID8; ISSN: 0142-2782
PB Wiley
DT Journal
LA English
AB The **hydrochloride** salt of **fexofenadine** (I), the primary **metabolite** of **terfenadine** (Seldane), is being developed for the treatment of symptoms assocd. with seasonal allergic rhinitis without producing sedation. Clin. safety and efficacy studies of -I-HCl were conducted using an immediate-relapse capsule formulation of the drug. A tablet contg. the same granulation plus magnesium stearate is being developed as a supplementary dosage form. Because co-ingestion of food has been shown to effect the bioavailability of many drugs, the present studies were conducted to evaluate bioavailability of I-HCl given as capsules or tablets when administered with a high-fat meal. Previous studies with I-HCl have shown that under fasted conditions the relative bioavailability of the capsule is 89-93%$ when compared to an oral soln. The bioequivalence of the tablets relative to the capsules has also been established under fasting conditions (unpublished data). Two sep. open-label, randomized crossover design studies were conducted where each subject received either (i) a single oral dose of 80 mg I-HCl prodn.-scale capsules (2.times.40 mg) following a 10 h fast and 30 min following a high-fat breakfast or (ii) a single oral dose of 120 mg I-HCl prodn.-scale immediate-relase tablets (3.times.40 mg) after a 10 h fast and after ingestion of a high-fat breakfast. The high-fat breakfast consisted of two eggs fried in butter, two strips of bacon, two pieces of buttered toast, 2 oz hash brown, and 8 oz whole milk (55 g fat, 33 g protein, 58 g carbohydrate). A 6d washout was allowed between treatment periods.

AN 1994:253379 CAPLUS
DN 120:253379
TI Pharmaceutical compositions containing terfenadine derivatives and their optically pure isomers for treating allergic disorders
IN Young, James W.; Gray, Nancy M.; Woosley, Raymond L.; Chen, Yiwang
PA Sepracor Inc., USA; Georgetown University
SO PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9403170	A1	19940217	WO 1993-US7260	19930803	<--
	W: AT, AU, BB, BG, BR, CA, CH, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE					
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG					
	GB 2284351	A1	19950607	GB 1995-2183	19930803	<--
	GB 2284351	B2	19961127			
	HU 71889	A2	19960228	HU 1995-313	19930803	<--
	EP 701443	A1	19960320	EP 1993-918584	19930803	<--
	EP 701443	B1	19980121			
	EP 701443	B2	20001122			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					
	AU 675240	B2	19970130	AU 1993-47986	19930803	<--
	AU 9347986	A1	19940303			
	EP 815860	A2	19980107	EP 1997-104837	19930803	<--
	EP 815860	A3	19980114			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE					
	AT 162399	E	19980215	AT 1993-918584	19930803	<--
	ES 2086270	T3	19980301	ES 1993-918584	19930803	<--
	PL 174373	B1	19980731	PL 1993-307339	19930803	<--
	BR 9306841	A	19981208	BR 1993-6841	19930803	<--
	JP 2000086512	A2	20000328	JP 1999-291216	19930803	
	JP 2000086516	A2	20000328	JP 1999-291230	19930803	
	JP 3037697	B2	20000424			
	JP 3041954	B2	20000515	JP 1994-505499	19930803	<--
	JP 08500348	T2	19960116			
	RO 116043	B1	20001030	RO 1995-160	19930803	
	CA 2141572	C	20010206	CA 1993-2141572	19930803	
	RU 2167657	C2	20010527	RU 1995-107881	19930803	
	EP 1214937	A2	20020619	EP 2002-6356	19930803	
	EP 1214937	A3	20021030			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE					
	US 5375693	A	19941227	US 1994-191061	19940202	<--
	NO 9500374	A	19950329	NO 1995-374	19950201	<--
	FI 9500467	A	19950331	FI 1995-467	19950202	<--
	AU 9671822	A1	19970130	AU 1996-71822	19961119	<--
	AU 9918429	A1	19990429	AU 1999-18429	19990225	
	JP 2000086513	A2	20000328	JP 1999-291220	19991013	
	JP 3288660	B2	20020604			
	JP 2000086514	A2	20000328	JP 1999-291223	19991013	
	JP 3288661	B2	20020604			
	JP 2000086515	A2	20000328	JP 1999-291228	19991013	
	JP 3288662	B2	20020604			
PRAI	US 1992-924156	A	19920803			
	US 1992-924182	A	19920803			
	EP 1993-918584	A3	19930803			
	EP 1997-104837	A3	19930803			
	JP 1994-505499	A3	19930803			
	WO 1993-US7260	W	19930803			

AU 1996-71822 A3 19961119

AB Pharmaceutical compns. comprising terfenadine or a salt thereof (Markush structure given), are used as antihistaminic agents which do not induce any significant cardiac arrhythmia. Thus, Me S-4-[1-oxo-4-(4-hydroxydiphenylmethyl-1-piperidinyl)buyl]-.alpha.,.alpha.-dimethylbenzeneacetacetate was reduced to obtain Me S-4-[1-hydroxy-4-(4-hydroxydiphenylmethyl-1-piperidinyl)buyl]-.alpha.,.alpha.-dimethylbenzeneacetacetate (I). I was refluxed with NaOH and EtOH for 7 hs and the residue was dissolved in water and the aq. soln. was acidified with glacial AcOH to provide S-terfenadine carboxylate (II). II at 10-9 concn. inhibited the binding of pyrilamine to histamine H1 receptors by 8.1%. A capsule contained I 30.0, starch-1500 69.0, Mg stearate 1.0mg.

```
=> s fexofenadi?(l)(powder? or liquid? or noncrystal? or amorph?)
          277 FEXOFENADI?
       519091 POWDER?
       727252 LIQUID?
         2928 NONCRYSTAL?
       225908 AMORPH?
L8          6 FEXOFENADI?(L)(POWDER? OR LIQUID? OR NONCRYSTAL? OR AMORPH?)

=> d bib abs 1-6

L8   ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2003 ACS
AN   2003:77336  CAPLUS
DN   138:126952
TI   Polymorphs of fexofenadine hydrochloride
IN   Dolitzky, Ben-Zion; Wizel, Shlomit; Krochmal, Barnaba; Diller, Dov; Gross,
     Irwin
PA   Israel
SO   U.S. Pat. Appl. Publ., 38 pp., Cont.-in-part of U. S. Ser. No. 118,807.
     CODEN: USXXCO
DT   Patent
LA   English
FAN.CNT 3
     PATENT NO.         KIND  DATE          APPLICATION NO.  DATE
     ---------------    ----  --------      ---------------  --------
PI   US 2003021849      A1    20030130      US 2002-133460   20020426
     US 2002177608      A1    20021128      US 2002-118807   20020408
     WO 2003039482      A2    20030515      WO 2002-US35996  20021108
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,
             LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,
             PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT,
             TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ,
             MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
             CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,
             NE, SN, TD, TG
PRAI US 2001-282521P    P     20010409
     US 2001-307752P    P     20010725
     US 2001-314396P    P     20010823
     US 2001-336930P    P     20011108
     US 2001-339041P    P     20011207
     US 2001-344114P    P     20011228
     US 2002-361780P    P     20020304
     US 2002-363482P    P     20020311
     US 2002-118807     A2    20020408
     US 2002-133460     A2    20020426
     US 2002-390198P    P     20020619
     US 2002-403765P    P     20020815
     US 2002-406214P    P     20020827
     US 2002-387670P    P     20021006
AB   The present invention provides novel crystal forms of fexofenadine
     hydrochloride Forms V, VI and VIII-XV and processes for their prepn. as
     well as prepn. of amorphous form and other cryst. forms of
     fexofenadine hydrochloride.  Forms XIV and XV are solvates of Et
     acetate, while Form IX is a solvate of MTBE or cyclohexane.  The forms are
     useful for administration to humans and animals to alleviate symptoms
     caused by histamine.  The present invention further provides
     pharmaceutical compns. of the new cryst. forms.

L8   ANSWER 2 OF 6  CAPLUS  COPYRIGHT 2003 ACS
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AN 2002:793365 CAPLUS
DN 137:316066
TI Polymorphs of fexofenadine hydrochloride
IN Dolitzky, Ben-Zion; Wizel, Shlomit; Krochmal, Barnaba; Diller, Dov; Gross, Irwin
PA Teva Pharmaceutical Industries Ltd., Israel; Teva Pharmaceuticals USA, Inc.
SO PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002080857	A2	20021017	WO 2002-US11251	20020408

PI
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI	US 2001-282521P	P	20010409
	US 2001-307752P	P	20010725
	US 2001-314396P	P	20010823
	US 2001-336930P	P	20011108
	US 2001-339041P	P	20011207
	US 2001-344114P	P	20011228
	US 2002-361780P	P	20020304
	US 2002-363482P	P	20020311

AB The present invention provides novel crystal forms of **fexofenadine** hydrochloride Forms (V, VI and VIII through XV) and processes for their prepn. and prepn. of **amorphous** form and other cryst. forms of **fexofenadine** hydrochloride. Forms (XIV and XV) are solvates of Et acetate, while Form IX is anhyd., but can be crystd. as solvate of MTBE or cyclohexane. The forms are useful for administration to humans and animals to alleviate symptoms caused by histamine. The present invention further provides pharmaceutical compns. of the new cryst. forms, e.g., capsules and tablets.

L8 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2003 ACS
AN 2002:658079 CAPLUS
DN 137:201234
TI Method for producing nonhydrated antiallergic fexofenadine hydrochloride in a novel crystalline form
IN Kirsch, Volker
PA Cilag A.-G., Switz.
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA German
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002066429	A1	20020829	WO 2002-CH27	20020117

PI
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,

UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRAI CH 2001-329 A 20010223
OS CASREACT 137:201234
AB A nonhydrated **fexofenadine** hydrochloride is obtained from **fexofenadine** base and hydrogen chloride either in the form of a novel crystal polymorph, in an **amorphous** form, or in the form of a mixt. of different polymorphs. The novel polymorph can be used as a therapeutically active ingredient and can be processed to form a pharmaceutical contg. the same and a pharmaceutically acceptable carrier suitable for use as an antihistaminic agent, an antiallergic agent, and/or a bronchodilating agent.
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2003 ACS
AN 2002:56462 CAPLUS
DN 136:144597
TI Determination of **fexofenadine** in human plasma and urine by **liquid** chromatography-mass spectrometry
AU Hofmann, Ute; Seiler, Monika; Drescher, Siegfried; Fromm, Martin F.
CS Dr. Margarete Fischer-Bosch-Institut fur Klinische Pharmakologie, Stuttgart, D-70376, Germany
SO Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2002), 766(2), 227-233
CODEN: JCBAAI; ISSN: 1570-0232
PB Elsevier Science B.V.
DT Journal
LA English
AB A sensitive method was developed to det. fexofenadine in human plasma and urine by HPLC-electrospray mass spectrometry with MDL 026042 as internal std. Extn. was carried out on C18 solid-phase extn. cartridges. The mobile phases used for HPLC were: (A) 12 mM ammonium acetate in H2O and (B) MeCN. Chromatog. sepn. was achieved on a LUNA CN column (10 cm.times.2.0 mm I.D., particle size 3 .mu.m) using a linear gradient from 40% B to 60% B in 10 min. The mass spectrometer was operated in the selected ion monitoring mode using the resp. MH+ ions, m/z 502.3 for fexofenadine and m/z 530.3 for the internal std. The limit of quantification achieved with this method was 0.5 ng/mL in plasma and 1.0 ng in 50 .mu.L of urine. The method described was successfully applied to the detn. of fexofenadine in human plasma and urine in pharmacokinetic studies.
RE.CNT 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2003 ACS
AN 2001:81754 CAPLUS
DN 134:136804
TI Simultaneous determination of **fexofenadine** hydrochloride and pseudoephedrine sulfate in pharmaceutical dosage [forms] by reversed-phase high-performance **liquid** chromatography
AU Zarapkar, S. S.; Bhandari, N. P.; Halkar, U. P.
CS Dept. of Chemistry, D.G. Ruparel College, Mumbai, 400 016, India
SO Indian Drugs (2000), 37(9), 421-425
CODEN: INDRBA; ISSN: 0019-462X
PB Indian Drug Manufacturers' Association
DT Journal
LA English
AB A simple, fast and precise reversed-phase HPLC method for the simultaneous detn. of fexofenadine and pseudoephedrine in tablets was based on a 5-.mu.

Inertsil C8 column in an isocratic mode with a mobile phase of pH 3.5 0.025M H3PO4-MeCN (60:40). The flow rate was 1.0 mL/min and the effluent was monitored at 215 nm. Methylparaben was used as an internal std. The limit of detection was 0.5 and 5 .mu.g/mL of pseudoephedrine and fexofenadine, resp. The recovery was close to 100%.

RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS
AN 2000:841983 CAPLUS
DN 134:21436
TI Preparation of **amorphous fexofenadine** hydrochloride using solvent method and spray or freezing drying techniques
IN Kumar, Naresh; Khanduri, Chandras Has; Sharma, Mukesh
PA Ranbaxy Laboratories Limited, India
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000071124	A1	20001130	WO 2000-IB708	20000525
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1185266	A1	20020313	EP 2000-927651	20000525
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRAI IN 1999-DE776 A 19990525
WO 2000-IB708 W 20000525

AB This invention relates to the prepn. of **amorphous** form of **fexofenadine** hydrochloride (I) and to a compn. contg. it. The process for prepn. of **amorphous** form of I comprises (1) dissolving cryst. I in the lower alkanol solvent such as methanol, or in the ketone solvent such as acetone, or in the chlorinated solvent such as chloroform, and (2) recovering **amorphous** I by spray drying or freeze drying technique.

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

AN 1989:179429 CAPLUS
DN **110:179429**
TI Physico-pharmaceutical studies on 9,3"-diacetylmidecamycin. Part 3. Amorphous formation of 9,3"-diacetylmidecamycin by freeze drying and through grinding
AU Sato, Toyomi; Ishiwata, Mayumi; Nemoto, Satoru; Yamaguchi, Hiroyuki; Kobayashi, Toshiyuki; Sekiguchi, Keiji; Tsuda, Yasuyuki
CS Pharm. Dev. Lab., Meiji Seika Kaisha, Ltd., Kawasaki, 210, Japan
SO Yakuzaigaku (1988), 48(4), 296-304
CODEN: YAKUA2; ISSN: 0372-7629
DT Journal
LA English
AB Prepn. of amorphous solid of 9,3''-diacetylmidecamycin (I) was attempted by applying the freeze drying method and grinding process. Freeze-dried I was.. Ground I was. The freeze-dried I, prepd. by freeze drying of a dioxane soln. of I, was a pure amorphous solid, whereas ground I, prepd. through grinding without any additive in a vibration mill up to 20 h, could not be converted to entire amorphous state. Soly. of freeze-dried I was almost the same as that of the spray-dried amorphous I reported previously.

=> s l1(l)amorph?
225908 AMORPH?
L4 5 L1(L)AMORPH?

=> d bib abs 1-5

L4 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 2000:786497 CAPLUS
DN 134:357438
TI Application of microcalorimetry in the pharmaceutical technology. Part I. Characterization of solid pharmaceuticals by heats of solution and crystallization measurement
AU Yonemochi, Etsuo; Yoshihashi, Yasuo; Terada, Katsuhide
CS School of Pharmaceutical Sciences, Toho University, Funabashi, Chiba, 274-8510, Japan
SO Pharm Tech Japan (1999),.15(5), 723-726, 729-731
CODEN: PTJAE9; ISSN: 0910-4739
PB Yakugyo Jihosha
DT Journal; General Review
LA Japanese
AB A review with 9 refs. This review describes an approach of microcalorimetry to the characterization of pharmaceutical solids. The heats of soln. of indomethacin polymorphs were measured in a microcalorimeter. The heat of transition from .alpha.- to .gamma.-form was precisely obtained. The disordered levels of **amorphous** clarithromycin, ursodeoxychalic acid and **terfenadine** obtained by grinding and **spray** drying were evaluated by using the heat of soln. measurement. The heat of soln. of **amorphous** samples was greater than that of cryst. sample. A good correlation was obsd. between crystallinity and heat of soln. for the partially **amorphous** samples. The relationship between crystallinity and logarithm of dissoln. rate was derived, and a linear correlation was obtained. The heat of crystn. was studied for low degree of **amorphous** content **powders**. The microcalorimetry showed the ability to detect the existence of **amorphous** material even for mixts. which contain less than 1% wt./wt. The deconvolution theory was applied to the microcalorimetric data for kinetic study of dissoln. rate. The dissoln. profile was calcd. from the calorimetric traces for the heat of diln. and the heat of soln. by a numerical deconvolution. The disintegration and dissoln. mechanisms of tablet were estd. from the dissoln. rate profile obtained by the calorimetric method.

L4 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 2000:688760 CAPLUS
DN 133:366289
TI Quantitative correlation between initial dissolution rate and heat of fusion of drug substance
AU Yoshihashi, Yasuo; Kitano, Harumi; Yonemochi, Etsuo; Terada, Katsuhide
CS Department of Pharmaceutics, School of Pharmaceutical Sciences, Toho University, Chiba, 274-8510, Japan
SO International Journal of Pharmaceutics (2000), 204(1-2), 1-6
CODEN: IJPHDE; ISSN: 0378-5173
PB Elsevier Science B.V.
DT Journal
LA English
AB The initial dissoln. rates of **amorphous**, partial cryst. and cryst. samples of **terfenadine** polymorphs (forms I and II) were measured by the rotating disk method. The heats of fusion due to cryst. fraction of samples were obtained by the DSC data taking into account the heat of crystn. and the heat capacity change at glass transition during the heating process. The logarithms of initial dissoln. rates of different crystallinity samples were linearly correlated with the cor.

heats of fusion, irresp. of the crystal forms.
RE.CNT 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 1998:719430 CAPLUS
DN 130:86230
TI Evaluation of crystallinity and amorphous of drug substance by thermal analysis
AU Terada, Katsuhide; Yoshihashi, Yasuo
CS Sch. Pharm. Sci., Toho Univ., Funabashi, 274-8510, Japan
SO Netsu Sokutei (1998), 25(4), 105-110
CODEN: NESOD2; ISSN: 0386-2615
PB Nippon Netsu Sokutei Gakkai
DT Journal; General Review
LA Japanese
AB A review with 10 refs. Crystallinity of drug substance was evaluated by **powder** x-ray diffraction methods and thermal methods, DSC and microcalorimetry. **Terfenadine** was used as drug substance and different crystallinity samples were prepd. by grinding. The crystallinity of **terfenadine** decreased with the increase in grinding time. The dissoln. rates were increased as the crystallinity of **terfenadine** decreased. Linear correlation was obtained between crystallinity and logarithm of dissoln. rate of **terfenadine**. Esp., the crystallinity obtained by the thermal methods was well linearly correlated with soly. data in almost all crystallinity region. It was confirmed that the thermal methods were useful for the quality control of crystallinity of drug substance. Thermal method is also efficient for the characterization of **amorphous** state.

L4 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 1995:406689 CAPLUS
DN 122:170217
TI Neomorphic ibuprofen and methods of using same
IN Geyer, Robert P.; Tuliani, Vinod V.
PA Ibah, Inc., USA
SO PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9501321	A1	19950112	WO 1994-US6600	19940622
	W: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5310960	A	19940510	US 1993-86922	19930702
	US 5310961	A	19940510	US 1993-87573	19930702
	US 5466865	A	19951114	US 1993-169672	19931217
	AU 9473951	A1	19950124	AU 1994-73951	19940622
PRAI	US 1993-86922		19930702		
	US 1993-87573		19930702		
	US 1993-169672		19931217		
	WO 1994-US6600		19940622		

AB A novel neomorphic form of ibuprofen, processes for prepg. the ibuprofen, and method for administering the ibuprofen are provided. The neomorphic form is characterized by having a distinctively less bitter taste and caused less burning sensation upon swallowing. The neomorphic form of ibuprofen contains an amorphous ibuprofen which exhibits no birefringence. Tests indicate that the neomorphic form is less irritating to the

gastrointestinal tract of animals upon administration. For example, conventional ibuprofen was heated to molten state at 77-80.degree. and cooled to 0.degree. in a pliable plastic container and the vessel was struck repeatedly by a hammer to induce the supercooled ibuprofen to resolidify. The resolidified amorphous ibuprofen had an improved taste and a decreased burning sensation in comparison to the conventional ibuprofen.

L4 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 1992:46212 CAPLUS
DN 116:46212
TI Some formulation aspects of terfenadine solid dispersions
AU Badwan, A. A.; Abu-Malooh, A.; Owais, Lina; Salem, M. Sheikh; Alkaysi, H. N.; Arafat, T. A.
CS Jordanian Pharm. Manuf. Co. Ltd., Naor, Jordan
SO European Journal of Pharmaceutics and Biopharmaceutics (1991), 37(3), 166-70
CODEN: EJPBEL; ISSN: 0939-6411
DT Journal
LA English
AB Solid dispersions of **terfenadine** (I) in polyethylene glycol (PEG) and poly(vinylpyrrolidone) (PVP) were prepd. by the solvent method and the coevaporates characterized by x-ray **powder** diffraction and DSC. **Amorphous** I was detected in dispersions contg. <15% of the drug. In dispersions contg. higher concns., both glassy and cryst. forms were present. The dissoln. of dispersions prepd. with different mol. wts. of PEG showed differences at 15, but not at 45 min. PEG-showed higher dissoln. rates than PVP-based prepns. An increase of the carrier-drug ratio retarded the dissoln., which was attributed to a phys. hindrance of drug release.

Eli Lilly and Co. v. Barr Laboratories Inc., 58 USPQ2d 1869 (CA FC 2001)

58 USPQ2D 1869
Eli Lilly and Co. v. Barr Laboratories Inc.

U.S. Court of Appeals Federal Circuit

Nos. 99-1262, -1263, -1264, -1303
Decided May 30, 2001

Headnotes

PATENTS

[1] Patentability/Validity — Specification — Best mode (§115.1107)

Patents for pharmaceutical compositions do not violate best mode requirement of 35 U.S.C. §112 by failing to disclose inventor's preferred method for synthesizing starting material, since neither patent claims starting material itself or method for making it, and best mode requirement does not compel disclosure of inventor's unclaimed method of synthesis, and since starting material in question was commercially available and described in prior art, and thus was not novel subject matter that required inventor to disclose method by which it could be obtained.

[2] Patentability/Validity — Specification — Best mode (§115.1107)

Patents for pharmaceutical compositions do not violate best mode requirement of 35 U.S.C. §112 by failing to disclose particular recrystallization solvent inventor used to purify claimed composition, even though best mode of clamed invention involves purification through recrystallization, since neither patent claims recrystallization process or recrystallization solvent, and failure to disclose preferred solvent thus does not equate to best mode violation, and since patentee's failure to disclose unclaimed preferred mode for accomplishing routine detail does not violate best mode requirement if, as in present case, those skilled in art are aware of alternative means for accomplishing routine detail that would still produce best mode of practicing claimed invention.

[3] Patentability/Validity — Anticipation — Double patenting (§115.0708)

Obviousness-type double patenting analysis first requires court, as matter of law, to construe claim in earlier patent and claim in later patent and determine differences between them, and to then determine whether differences in subject matter between claims is such that claims are patentably distinct; later claim that is not patentably distinct from earlier claim in commonly-owned patent is invalid, and later claim is not patentably distinct if it is obvious over, or anticipated by, earlier claim.

[4] Patentability/Validity — Anticipation — Double patenting (§115.0708)

Claim of patent for method of administering fluoxetine hydrochloride to inhibit serotonin uptake in animals is invalid, for double patenting, over earlier claim for method of treating anxiety in humans by administering effective amount of fluoxetine or pharmaceutically acceptable salt thereof, since person of ordinary skill would have recognized that fluoxetine hydrochloride is pharmaceutically acceptable salt of fluoxetine, since serotonin uptake inhibition is inherent property of fluoxetine hydrochloride upon its administration, and there is consequently no patentable distinction between administering fluoxetine hydrochloride for treatment of anxiety and inhibition of serotonin uptake by administration of fluoxetine hydrochloride, since humans are species of animal genus, and since later genus claim is anticipated by, and therefore not patentably distinct from, earlier species claim.

Particular Patents

Particular patents — Chemical — Antidepressant drugs

4,314,081, Molloy and Schmiegel, aloxyphenylpropylamines, not invalid.

4,626,549, Molloy and Schmiegel, treatment of obesity with aloxyphenylpropylamines, claim 7 invalid.

Case History and Disposition
Appeal from the U.S. District Court for the Southern District of Indiana, Barker, C.J.

Consolidated actions by Eli Lilly & Co. against Barr Laboratories Inc., Apotex Inc., Bernard C. Sherman, Geneva Pharmaceuticals Inc., and Interpharm Inc. for patent infringement. Defendants Barr Laboratories Inc., Apotex Inc., Bernard C. Sherman, and Geneva Pharmaceuticals Inc. appealed from summary judgment that patents in suit are not invalid, and plaintiff cross-appealed from ruling that defendants are entitled to jury trial on invalidity counterclaims. Summary judgment on validity issue was affirmed in part and reversed in part, and ruling on defendants' right to jury trial was vacated (55 USPQ2d 1609). Petition for rehearing en banc was granted, panel opinion was vacated, and appeals were reassigned to same panel for specific revision of section on double patenting (58 USPQ2d 1865). On reassignment, district court's decision is affirmed in part, reversed in part, and vacated in part.

Attorneys:
Charles E. Lipsey, Allen M. Sokal, Kenneth M. Frankel, L. Scott Burwell, and David S. Forman, of Finnegan, Henderson, Farabow, Garrett &Dunner, Washington, D.C.; Douglas K. Norman and James P. Leeds, of Eli Lilly and Co., Indianapolis, Ind., for plaintiff-cross appellant.

Richard S. Clark, Rochelle K. Seide, Marta E. Delsignore, Louis Sorell, Robert Neuner, and Thomas J. Parker, of Baker & Botts, New York, N.Y., for defendant-appellant Geneva Pharmaceuticals Inc.

George C. Lombardi, James F. Hurst, Dan K. Webb, Bradley C. Graveline, Christine J. Siwik, Taras A. Gracey, and Derek John Sarafa, of Winston & Strawn, Chicago, Ill.; Mark E. Waddell, of Bryan Cave, New York, for defendant-appellant Barr Laboratories Inc.

Hugh L. Moore and Diane I. Jennings, of Lord, Bissell &Brook, Chicago, for defendants-appellants Apotex Inc. and Bernard C. Sherman.

Judge:
Before Mayer, chief judge, Friedman, senior circuit judge, and Gajarsa, circuit judge.

Opinion Text

Opinion By:
Gajarsa, J.

ORDER

On the petition for rehearing or rehearing *en banc*, the court accepted the petition for rehearing *en banc*. Acting *en banc*, the court vacated the panel's original opinion entered on August 9, 2000, which is reported at 222 F.3d 973, 55 USPQ2d 1609 (Fed. Cir. 2000). The *en banc* court reassigned the opinion to the panel for a specific revision of the double patenting section. Based on the conclusions of the panel, the panel's original judgment affirming the district court's determination on the issue of best mode is reaffirmed. The panel's original judgment, which reversed the district court's determination that claim 7 of U.S. Patent No. 4,626,549 ("the '549 patent") is not invalid for double patenting, is reaffirmed, but on a different legal basis.

In December 1995, Barr Laboratories, Inc. ("Barr") filed an Abbreviated New Drug Application ("ANDA") under the Hatch-Waxman Act, *see* 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (1994), seeking approval from the Food and Drug Administration ("FDA") to market fluoxetine hydrochloride as an antidepressant. Fluoxetine hydrochloride is the active ingredient in Eli Lilly and Company's ("Lilly's") antidepressant drug Prozac. Lilly, on April 10, 1996, pursuant to 35 U.S.C. §271(e)(2)(A) (1994), brought an infringement action in the United States District Court for the Southern District of Indiana, alleging that Barr's ANDA application infringed claim 5 of U.S. Patent No. 4,314,081 ("the '081 patent") and claim 7 the '549 patent. Lilly subsequently brought infringement actions against Geneva Pharmaceuticals, Inc., Apotex, Inc., and Bernard C. Sherman, all of whom had also filed ANDA applications with the FDA, and the actions were consolidated.

Barr and the other defendants (collectively "Barr") argued, *inter alia*, that claim 5 of the '081 patent and claim 7 of the '549 patent are invalid for failure to comply with the best mode requirement and that claim 7 of the '549 patent is invalid for double patenting. On cross-motions for summary judgment, the district court held in favor of Lilly, concluding that neither claim violates the best mode requirement and that no double patenting

exists.1 Barr appeals the district court's summary judgment rulings, and Lilly cross-appeals the district court's ruling that Barr was entitled to a jury trial on its invalidity counterclaims. Because we hold that both claims comply with the best mode requirement but that claim 7 of the '549 patent is invalid for obviousness-type double patenting, we affirm-in-part and reverse-in-part. Accordingly, we also vacate the district court's ruling that Barr is entitled to a jury trial because we dispose of the validity issues on appeal.

I. BACKGROUND

The present appeal concerns the validity of claim 5 of the '081 patent, which covers the pharmaceutical compound fluoxetine hydrochloride—the active ingredient in Lilly's antidepressant drug Prozac—and claim 7 of the '549 patent, which covers the administration of fluoxetine hydrochloride to inhibit serotonin uptake in an animal's brain neurons.

On January 10, 1974, Lilly filed application Serial No. 432,379 ("the '379 application") containing claims for a class of compounds, therapeutic methods of using those compounds, and pharmaceutical compositions comprising those compounds. The '379 application named Bryan B. Molloy ("Molloy") and Klaus K. Schmiegel as inventors. After its filing, the '379 application engendered a progeny of divisional applications, continuation applications, and patents that rivals the Hapsburg legacy. When the last patent stemming from the '379 application issued in December 1986, the application had spawned four divisional applications, three continuation applications, and six patents. During that twelve-year period, Lilly obtained six patents relating to fluoxetine hydrochloride—the '081 and '549 patents, as well as U.S. Patent Nos. 4,018,895 ("the '895 patent"), 4,194,009 ("the '009 patent"), 4,590,213 ("the '213 patent"), and 4,329,356 ("the '356 patent"). The '213 and '356 patents did not stem from the '379 application, and during the course of this litigation, Lilly disclaimed those patents.

The '009 patent, which expired in April 1994, claimed a class of pharmaceutical compounds, including fluoxetine hydrochloride, for administration in pyschotropically effective amounts. The '895, '213, and '356 patents related to methods for treating particular ailments by administering a pharmaceutical compound within a class of compounds that includes fluoxetine hydrochloride. Specifically, the '895 patent, which expired in April 1994, concerned the treatment of humans suffering from depression; the '213 patent concerned the treatment of humans suffering from anxiety; and the '356 patent concerned the treatment of animals suffering from hypertension.

In December 1995, pursuant to a Paragraph IV certification under the Hatch-Waxman Act, *see* 21 U.S.C. §355(j)(2)(A)(vii)(IV),2Barr filed an ANDA application seeking FDA approval to market fluoxetine hydrochloride as an antidepressant. Lilly responded by bringing an action in district court under 35 U.S.C. §271(e)(2)(A),3 asserting that Barr's ANDA application infringed claim 7 of the '549 patent and claim 5 of the '081 patent.

At the district court, Barr argued that both claims are invalid for failure to comply with the best mode requirement and that claim 7 of the '549 patent is invalid for obviousness-type double patenting. With regard to the best mode issue, Barr advanced two independent arguments. First, Barr argued that the claims are invalid because the patents failed to disclose Molloy's preferred method for synthesizing p-trifluoromethylphenol—a starting material necessary to make fluoxetine hydrochloride. Second, Barr argued that the claims are invalid because the patents failed to disclose Molloy's preferred solvent for recrystallizing fluoxetine hydrochloride. With regard to the issue of double patenting, Barr advanced three independent arguments, contending that claim 7 of the '549 patent is invalid in light of

(1) the '356 and '213 patents, (2) the '895 and '009 patents, and (3) the '081 patent.

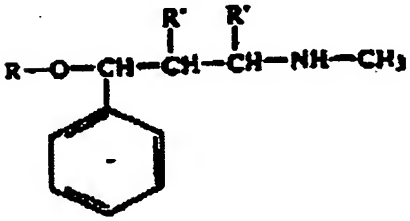
On cross motions for summary judgment, the district court held in favor of Lilly, concluding that claim 5 of the '081 patent and claim 7 of the '549 patent do not violate the best mode requirement and that claim 7 is not invalid for double patenting under any of Barr's theories. The district court recognized that Barr contended that claim 7 of the '549 patent is invalid for double patenting over, *inter alia*, the '213 patent because it merely sets forth the "scientific explanation"for the subject matter of that and other Lilly patents. Yet, the district court determined that Barr failed to provide any authoritative, reliable scientific opinion to establish that claim 7 of the '549 patent constitutes merely the scientific explanation of what was already claimed in the patents that came before it, including the '213 patent.

This appeal followed. Because these issues concern disparate parts of the record evidence, we describe separately the background relevant to each argument.

The Claims at Issue

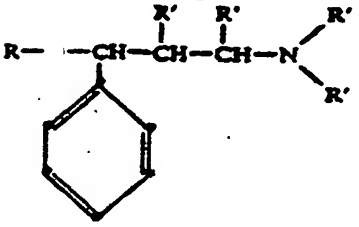
A. Claim 5 of the '081 patent

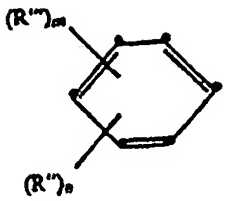
Stemming directly from the '379 application, the '081 patent issued on February 2, 1982. Claim 5 of the '081 patent, which depends from claim 1, covers the compound N-methyl 3-(p-trifluoromethylphenoxy)-3-phenylpropylamine hydrochloride—commonly referred to as fluoxetine hydrochloride—and pharmaceutically-acceptable acid addition salts thereof formed with non-toxic acids. Claim 1, in turn, provides as follows:

> A compound of the formula
>
> 
>
> wherein each R' is independently H or CH_3 and R is m- or p-chlorophenyl, o-, m-, or p-methoxyphenyl, phenyl, o- or m-fluorophenyl, o- or p-tolyl, 2,4-difluorophenyl or p-trifluoromethylphenyl and acid addition salts formed with pharmaceutically-acceptable acids.

B. Claim 7 of the '549 patent

On March 31, 1986, Lilly filed continuation-in-part application Serial No. 846,448, claiming the benefit of the 1974 filing date of the '379 application under 35 U.S.C. § 120.4 On December 2, 1986, the application matured into the '549 patent. Claim 7 of the '549 patent, which depends on claim 4, relates to blocking the uptake of the monoamine serotonin in an animal's brain neurons through administration of the compound N-methyl-3-(p-trifluoromethylphenoxy)-3-phenylpropylamine hydrochloride—commonly referred to as fluoxetine hydrochloride. Claim 4 provides as follows:

> A method of blocking the uptake of monoamines by brain neurons in animals comprising administering to said animal a monoamine blocking amount of a compound of the formula
>
> 
>
> wherein each R' is independently hydrogen or methyl; wherein R is naphthyl or



wherein R" and R"' are halo, trifluoromethyl, C_1 -C_4 alkyl, C_1-C_3 alkyloxy or C_3 -C_4 alkenyl; and wherein n and m are 0, 1 or 2; and acid addition salts thereof formed with pharmaceutically-acceptable acids.

C. Best Mode: p-trifluoromethylphenol

Both the '081 and '549 patents identify p-trifluoromethylphenol as a starting material for making fluoxetine hydrochloride. During the early stages of experimentation, Molloy used commercial p-trifluoromethylphenol purchased from Marshallton Research Laboratories. However, when large quantities of p-trifluoromethylphenol were necessary for clinical testing, Lilly's division director refused to purchase p-trifluoromethylphenol due to the high costs. Instead, he required that Molloy and his colleagues synthesize their own p-trifluoromethylphenol.

To that end, Molloy worked with Lilly scientist Edward Lavagnino ("Lavagnino") to devise a cost-efficient method of synthesizing p-trifluoromethylphenol. After experimenting with various prior art methods, Molloy concluded that those methods were inadequate for generating a sufficient amount of p-trifluoromethylphenol for use in clinical testing. Then, following further research, Molloy and Lavagnino developed their own method for preparing p-trifluoromethylphenol that, as Lavagnino described in his deposition, was "superior"because it used "real cheap" starting material "available [in] tank car quantities." Also, in an article written after the filing of the `379 application, Molloy described his new synthesizing method as an improvement over prior art, because the "literature methods for [p-trifluoromethylphenol's] preparation are cumbersome and not easily adapted to large scale operations."

The '081 and '549 patents do not claim the material p-trifluoromethylphenol or a method for synthesizing it, nor do they disclose Molloy's method for synthesizing it.

D. Best Mode: Recrystallization

While experimenting with compounds claimed in the '081 and '549 patents, Molloy recrystallized the compounds in order to remove impurities and enhance their suitability for pharmaceutical use. The recrystallization process involved using a solvent to dissolve a sample of the compound and then separating the desired product in crystalline form from the impurities that remained dissolved. Between February 1973 and January 1974, Molloy and other Lilly scientists experimented with various solvents for recrystallizing fluoxetine hydrochloride and eventually found a particular solvent that produced a higher yield and higher purity than other solvents.

The record evidence illustrates that while Lilly scientists knew that some solvents for recrystallizing fluoxetine hydrochloride were more effective than others, choosing a suitable recrystallization solvent was well known to one of ordinary skill in the art. In particular, Dr. Elias J. Corey ("Corey"), a Nobel laureate, testified that fluoxetine hydrochloride is "generally quite easy to purify by recrystallizaton." Corey also explained that, although it requires some experimentation, selecting a recrystallization solvent is "very straightforward." Further, Barr's expert testified that "in 1974, sometimes the recrystallization of amine hydrochlorides was indeed routine."

The '081 and '549 patents do not claim a process for recrystallizing fluoxetine hydrochloride nor do they disclose any solvents for use in the recrystallizing fluoxetine hydrochloride.

E. Double Patenting: The '213 patent

On May 20, 1986, the '213 patent issued from an application filed on April 8, 1983. Claim 1 of the '213 patent provides:

> A method for treating anxiety in a human subject in need of such treatment which comprises the administration to such human an effective amount of fluoxetine or norfluoxetine or pharmaceutically acceptable salts thereof.

II. STANDARD OF REVIEW

We review a district court's grant of summary judgment *de novo*. *Conroy v. Reebok Int'l, Ltd.*, 14 F.3d 1570, 1575, 29 USPQ2d 1373, 1377(Fed. Cir. 1994). Summary judgment is appropriate when, based on the record, no genuine issue exists as to any material fact, and the moving party is entitled to judgment as a matter of law. *See* Fed. R. Civ. P. 56(c). A genuine issue exists if the evidence is such that a reasonable jury could find for the nonmoving party. *Anderson v. Liberty Lobby, Inc.*, 477 U.S. 242, 248 (1986); *General Mills, Inc. v. Hunt-Wesson, Inc.*, 103 F.2d 978, 980, 41 USPQ2d 1440, 1442(Fed. Cir. 1997).

A disputed fact is material if it might affect the outcome of the suit such that a finding of that fact is necessary and relevant to the proceeding. *Anderson*, 477 U.S. at 248; *General Mills*, 103 F.2d at 980, 41 USPQ2d at 1442.

When evaluating a motion for summary judgment, the court views the record evidence through the prism of the evidentiary standard of proof that would pertain at a trial on the merits. *Anderson*, 477 U.S. at 252-53. Under the patent statutes, a patent enjoys a presumption of validity, *see* 35 U.S.C. §282 , which can be overcome only through clear and convincing evidence, *see United States Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1563, 41 USPQ2d 1225, 1232(Fed. Cir. 1997). Thus, a moving party seeking to invalidate a patent at summary judgment must submit such clear and convincing evidence of invalidity so that no reasonable jury could find otherwise. Alternatively, a moving party seeking to have a patent held not invalid at summary judgment must show that the nonmoving party, who bears the burden of proof at trial, failed to produce clear and convincing evidence on an essential element of a defense upon which a reasonable jury could invalidate the patent. In determining whether a genuine issue of material fact exists, the court views the evidence in the light most favorable to the nonmoving party and resolves all doubts in its favor. *Anderson*, 477 U.S. at 255; *Transmatic, Inc. v. Gulton Indus., Inc.*, 53 F.3d 1270, 1274, 35 USPQ2d 1035, 1038(Fed. Cir. 1995).

III. BEST MODE

Pursuant to §112, ¶ 1, a patent specification must set forth the "best mode contemplated by the inventor of carrying out his invention." 35 U.S.C. §112, ¶ 1 (1994). The best mode requirement creates a statutory bargained-for-exchange by which a patentee obtains the right to exclude others from practicing the claimed invention for a certain time period, and the public receives knowledge of the preferred embodiments for practicing the claimed invention. *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 1532, 3 USPQ2d 1737, 1742(Fed. Cir. 1987) (quoting *In re Gay*, 309 F.2d 769, 772, 135 USPQ 311, 315(CCPA 1962)).

Our case law explicating the best mode requirement focuses on a two-prong inquiry. *Chemcast Corp. v. Arco Indus. Corp.*, 913 F.2d 923, 927-28, 16 USPQ2d 1033, 1036-37 (Fed. Cir. 1990). First, the factfinder must determine whether, at the time of filing the application, the inventor possessed a best mode for practicing the invention. *Fonar Corp. v. General Elec. Co.*, 107 F.3d 1543, 1548, 41 USPQ2d 1801, 1804 (Fed. Cir. 1997); *United States Gypsum Co. v. National Gypsum Co.*, 74 F.3d 1209, 1212, 37 USPQ2d 1388, 1390(Fed. Cir. 1996). Second, if the inventor possessed a best mode, the factfinder must determine whether the written description disclosed the best mode such that one reasonably skilled in the art could practice it. *Fonar*, 107 F.3d at 1548, 41 USPQ2d at 1804; *U.S. Gypsum*, 74 F.3d at 1212, 37 USPQ2d at 1390. The first prong involves a subjective inquiry, focusing on the inventor's state of mind at the time of filing. *U.S. Gypsum*, 74 F.3d at 1212, 37 USPQ2d at 1390; *Chemcast*, 913 F.2d at 928, 16 USPQ2d at 1036. The second prong involves an objective inquiry, focusing on the scope of the claimed invention and the level of skill in the art. *U.S. Gypsum*, 74 F.3d at 1212, 37 USPQ2d at 1390; *Chemcast*, 913 F.2d at 928, 16 USPQ2d at 1036-37.

With respect to the second prong of the best mode requirement, the extent of information that an inventor must disclose depends on the scope of the claimed invention. *Engel Indus. v. Lockformer Co.*, 946 F.2d 1528, 1531, 20 USPQ2d 1300, 1302(Fed. Cir. 1991). Accordingly, an inventor need not disclose a mode for obtaining unclaimed subject matter unless the subject matter is novel and essential for carrying out the best mode of the invention. *Applied Med. Resources Corp. v. United States Surgical Corp.*, 147 F.3d 1374, 1377, 47 USPQ2d 1289, 1291(Fed. Cir. 1998). Furthermore, the best mode requirement does not extend to production details or routine details. *Young Dental Mfg. Co., Inc. v. Q3 Special Prods., Inc.*, 112 F.3d 1137, 1143, 42 USPQ2d 1589, 1594-95 (Fed. Cir. 1997). Production details, which do not concern the "quality or nature of the [claimed] invention," *see id.* at 1143, 42 USPQ2d at 1595, relate to commercial and manufacturing considerations such as equipment on hand, certain available materials, prior relationships with suppliers, expected volume of production, and costs, *see Wahl Instruments, Inc. v. Acvious, Inc.*, 950 F.2d 1575, 1581, 21 USPQ2d 1123, 1128(Fed. Cir. 1991) (explaining that a "step or source or technique considered `best'in a

manufacturing circumstance may have been selected for a non-`best mode' reason"). Routine details, on the other hand, implicate the quality and nature of invention, but their disclosure is unnecessary because they are readily apparent to one of ordinary skill in the art. *Young Dental*, 112 F.3d at 1143, 42 USPQ2d at 1595.

At the district court, Barr advanced two independent reasons for invalidating the '081 and '549 patents for failure to disclose the best mode: (1) Lilly failed to disclose Molloy's preferred method for synthesizing p-trifluoromethylphenol, and (2) it failed to disclose Molloy's preferred solvent for recrystallizing the fluoxetine hydrochloride compound. On cross-motions for summary judgment, the district court held in favor of Lilly. Barr appeals, and we address each argument in turn.

A. Synthesizing p-trifluoromethylphenol

Barr contends that claim 5 of the '081 patent and claim 7 of the '549 patent do not meet the best mode requirement because the patents fail to disclose Molloy's method for synthesizing p-trifluoromethylphenol. In the present case, even assuming that Molloy preferred his method for synthesizing p-trifluoromethylphenol to alternative means of obtaining the material, we hold that failure to disclose the synthesizing method does not contravene the best mode requirement.

[1] We begin our analysis by examining the scope of the claimed inventions. *See Engel Indus.*, 946 F.2d at 1531, 20 USPQ2d at 1302 ("The best mode inquiry is directed to what the applicant regards as his invention, which in turn is measured by the claims."). Claim 5 of the '081 patent covers a formula for the compound fluoxetine hydrochloride, and claim 7 of the '549 patent covers a method for blocking the uptake of serotonin by brain neurons through administering a dosage of fluoxetine hydrochloride. Example 1 in both the '081 and '549 patents identifies the chemical p-trifluoromethylphenol as a starting material for making fluoxetine hydrochloride. Neither patent, however, claims p-trifluoromethylphenol itself or a method for synthesizing it. Thus, while the best mode for developing fluoxetine hydrochloride involves use of p-trifluoromethylphenol, the claimed inventions do not cover p-trifluoromethylphenol and the patents do not accord Lilly the right to exclude others from practicing Molloy's method for synthesizing p-trifluoromethylphenol. As a result, the best mode requirement does not compel disclosure of Molloy's unclaimed method for synthesizing p-trifluoromethylphenol. Furthermore, the circumstances here are different from those in *Dana Corp. v. IPC Ltd.*, 860 F.2d 415, 418, 8 USPQ2d 1692 (Fed. Cir. 1988), and *Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 940-41, 15 USPQ2d 1321, 1328(Fed. Cir 1990), in which an inventor failed to disclose unclaimed subject matter that was necessary for carrying out the best mode of the invention. In the present case, Molloy disclosed his preference for using p-trifluoromethylphenol when making fluoxetine hydrochloride. What he did not disclose, nor was he required to do so, was the unclaimed method for synthesizing p-trifluoromethylphenol. *Cf. Randomex, Inc. v. Scopus Corp.*, 849 F.2d 585, 590, 7 USPQ2d 1050, 1054 (Fed. Cir. 1988) (finding no violation of best mode requirement by concealment of a preferred cleaning fluid formula when the claimed invention "neither added nor claimed to add anything to the prior art respecting cleaning fluid").

To be sure, if the best mode for carrying out a claimed invention involves novel subject matter, then an inventor must disclose a method for obtaining that subject matter even if it is unclaimed. *Applied Med. Resources Corp. v. United States Surgical Corp.*, 147 F.3d 1374, 1377, 47 USPQ2d 1289, 1291(Fed. Cir. 1998); *Wahl Instruments*, 950 F.2d at 1583-84, 21 USPQ2d at 1130. That, however, is not the case here. In the present case, the record insistently demonstrates that p-trifluoromethylphenol was commercially available at the time Lilly filed its original application. The record includes a product catalog from Marshallton Research Laboratories, dated January 1973, offering to sell p-trifluoromethylphenol. The record also contains an expert witness report explaining that p-trifluoromethylphenol was commercially available before 1974 from Aldrich Chemical Company. Additionally, the record includes prior art references that describe methods for preparing p-trifluoromethylphenol.

Barr contends that *Clayton v. Akiba*, 214 USPQ 374 (Bd. Pat. App. 1982), supports its position that Lilly was obligated to disclose the method for synthesizing p-trifluoromethylphenol. We do not find that argument persuasive.

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Clayton, aside from being non-binding on this court, involves facts that are inapposite to the present case. In *Clayton*, the claimed invention was a chemical compound, and the Board found that the inventor violated the best mode requirement by failing to disclose his method for preparing a necessary intermediate compound. *See id.* at 380-81. The Board's reasoning, however, hinged on the fact that the intermediate compound was "*itself admittedly a novel compound* ... and, thus, its preparation [was] part and parcel of `carrying out' the invention." *Id.* at 381 (emphasis added). Here, by contrast, the chemical p-trifluoromethylphenol, as explained above, was commercially available and described in the prior art.

Barr also seizes upon portions of the record evidence in an effort to establish a best mode violation. For example, Barr relies on Lavagnino's deposition testimony that Molloy's method for synthesizing p-trifluoromethylphenol used material "available in tank car quantities, real cheap chemical, and simple transformations." Barr also cites Lavagnino's statement explaining that Molloy's synthesizing method could be "scaled up" to produce large amounts of p-trifluoromethylphenol. Barr points to Molloy's own statement that "the relatively high cost"of p-trifluoromethylphenol "is a limiting factor in its use as a chemical intermediate," and that he preferred his synthesizing method because other methods were "cumbersome and not easily adapted to large scale operations." Finally, Barr relies on evidence that Lilly stopped purchasing p-trifluoromethylphenol after Molloy developed his synthesizing method.

Rather than establishing a best mode violation, this amalgam of evidence provides paradigmatic examples of production details that the law excepts from best mode disclosure. Indeed, this evidence relates to considerations of costs, volume, and available resources for manufacturing fluoxetine hydrochloride, all details that are superfluous to the best mode requirement. *See Wahl Instruments*, 950 F.2d at 1581-82, 21 USPQ2d 1128-29 (holding no best mode violation for failure to disclose a method chosen for reasons of cost and volume). In short, the reasons for using Molloy's synthesizing method were not linked to the intrinsic quality of fluoxetine hydrochloride, which is the thrust of the best mode requirement.

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B. Recrystallization Solvent

Barr also argues that claim 5 of the '081 patent and claim 7 of the '549 patent violate the best mode requirement because Molloy failed to disclose the particular recrystallization solvent that he used to purify fluoxetine hydrochloride. Even assuming that Molloy preferred a particular and specific recrystallization solvent to others, we hold that failure to disclose that solvent does not violate the best mode requirement.

[2] Once again, we begin our analysis with the scope of the claimed invention. *See Engel Indus.*, 946 F.2d at 1531, 20 USPQ2d at 1302. Claim 5 of the '081 patent covers the compound fluoxetine hydrochloride, and claim 7 of the '549 patent covers a method for administering it. Both patents teach that the preferred embodiment of fluoxetine hydrochloride is achieved by purifying the compound through recrystallization. Based on the record, there is no genuine issue that one of ordinary skill in the art possessed the requisite knowledge to select a solvent for recrystallizing fluoxetine hydrochloride. Even Barr's expert testified that "in 1974, sometimes the recrystallization of amine hydrochlorides was

indeed routine." Choosing a solvent for performing recrystallization, therefore, constitutes a routine detail that falls outside the ambit of the best mode disclosure. *See Young Dental*, 112 F.3d at 1144, 42 USPQ2d at 1595; *Fonar*, 107 F.3d at 1549, 41 USPQ2d at 1805 ("It is well established that what is within the skill of the art need not be disclosed to satisfy the best mode requirement as long as that mode is described.").

Barr contends that, even if choosing a solvent for recrystallization is a routine detail, the best mode requirement compels Molloy to disclose the particular and specific solvent he used in the recrystallization process. In effect, Barr argues that Molloy was obligated to disclose not only the preferred embodiment of the claimed invention, but also the preferred solvent for the unclaimed recrystallization process. Stated at a higher level of generality, Barr asserts that a patentee must disclose a preferred mode for carrying out an unclaimed routine detail. That position, however, is in conflict with the scope of the claims at issue, our prior decisions, and the purpose undergirding the best mode requirement.

As we have often said, "[i]t is concealment of the best mode of practicing the *claimed invention* that §112, ¶ 1 is designed to prohibit." *Chemcast*, 913 F.2d at 927, 16 USPQ2d at 1036 (emphasis added). Here, the patents disclose that the best mode of the claimed invention is fluoxetine hydrochloride that is purified through recrystallization. The patents, however, do not claim a process for purifying fluoxetine hydrochloride through recrystallization or a solvent for performing the recrystallization. Thus, failure to disclose a preferred solvent does not equate to a best mode violation because the patents simply do not claim a recrystallization process or a recrystallization solvent. *See Engel Indus.*, 946 F.2d at 1531, 20 USPQ2d at 1302 ("Unclaimed subject matter is not subject to the disclosure requirements of §112; the reasons are pragmatic: the disclosure would be boundless and the pitfalls endless."); *cf. Northern Telecom Ltd. v. Samsung Elecs. Co.*, 215 F.3d 1281, 1288, 55 USPQ2d 1065, 1070 (Fed. Cir. 2000) (holding no best mode violation when inventor did not disclose an unclaimed, preferred method for use of the claimed invention—thin-line etching—because the claim covered a general process of plasma etching and the patent described the best mode for carrying out that process).

Further, §112 requires only "an adequate disclosure of the best mode." *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1025-26 (Fed. Cir. 1991). It logically follows that a patentee's failure to disclose an unclaimed, preferred mode for accomplishing a routine detail does not violate the best mode requirement because one skilled in the art is aware of alternative means for accomplishing the routine detail that would still produce the best mode of the claimed invention. Indeed, Barr and other companies are able to recrystallize fluoxetine hydrochloride by using solvents different from the one Molloy used. In addition, our cases hold that a patentee complies with §112 even though some experimentation is necessary to practice the best mode. *See id.* (holding that best mode does not require a "guarantee that every aspect of the specification be precisely and universally reproducible"); *Scripps Clinic & Research Found. v. Genentech, Inc.*, 927 F.2d 1565, 1579-80 (Fed. Cir. 1991); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384-85, 231 USPQ 81, 94(Fed. Cir. 1986). In *Hybritech*, for example, this court held that the patentee did not violate §112, even though carrying out the best mode of the invention involved screening experiments that were laborious and time consuming, because screening methods were known in the art. 802 F.2d at 1384-85, 231 USPQ at 94. Similarly, in the present case, solvents for recrystallizing fluoxetine hydrochloride were known in the art, and simply because selecting a desired solvent may have required some experimentation, nondisclosure of Molloy's particular solvent does not rise to a best mode violation.

Moreover, the purpose behind the best mode requirement supports our conclusion. As we explained in *Amgen*, the best mode requirement establishes a *quid pro quo* whereby the patentee "must not receive the right to exclude others unless at the time of filing he has provided an adequate disclosure of the best mode." 927 F.2d at 1210, 18 USPQ2d at 1024. The best mode requirement, however, is a two-way street, and in the present case, the '081 and '549 patents do not grant Lilly the right to exclude others from practicing Molloy's method of recrystallization or from using his preferred solvent. Thus, it would be incongruous to require that Molloy disclose that information nonetheless. *See Randomex*, 849 F.2d at 588, 7 USPQ2d at 1053 ("It is concealment of the best mode of practicing the *claimed invention* that section 112, ¶ 1 is designed to prohibit." (emphasis in original)).

In sum, because no genuine issue of material fact exists upon which a reasonable jury could find that claim 5 and claim 7 did not comply with the best mode requirement, we affirm the district court's grant of summary judgment in favor of Lilly. Thus, we have no occasion to determine if Barr has a right to a jury trial on that issue.

III. DOUBLE PATENTING

Through a statutorily prescribed term, Congress limits the duration of a patentee's right to exclude others from practicing a claimed invention. 35 U.S.C. §154(a)(2) (1994). The judicially-created doctrine of obviousness-type double patenting cements that legislative limitation by prohibiting a party from obtaining an extension of the right to exclude through claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent. *In re Longi*, 759 F.2d 887, 892, 225 USPQ 645, 648

(Fed. Cir. 1985) (explaining that, even though no explicit statutory basis exists for obviousness-type double patenting, the doctrine is necessary to prevent a patent term extension through claims in a second patent that are not patentably distinct from those in the first patent).5 As one of our predecessor courts explained, "[t]he fundamental reason for the rule [of obviousness-type double patenting] is to prevent unjustified timewise extension of the right to exclude granted by a patent no matter how the extension is brought about." *In re Van Ornum*, 686 F.2d 937, 943-44, 214 USPQ 761, 766(CCPA 1982) (quoting *In re Schneller*, 397 F.2d 350, 158 USPQ 210, 214(CCPA 1968)).

[3] Generally, an obviousness-type double patenting analysis entails two steps. First, as a matter of law, a court construes the claim in the earlier patent and the claim in the later patent and determines the differences.6 *Georgia-Pacific Corp. v. United States Gypsum Co.*, 195 F.3d 1322, 1326, 52 USPQ2d 1590, 1593(Fed. Cir. 1999). Second, the court determines whether the differences in subject matter between the two claims render the claims patentably distinct. *Id.* at 1327, 52 USPQ2d at 1595. A later claim that is not patentably distinct from an earlier claim in a commonly owned patent is invalid for obvious-type double patenting. *In re Berg*, 140 F.3d 1428, 1431, 46 USPQ2d 1226, 1229(Fed. Cir. 1998). A later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim. *In re Longi*, 759 F.2d at 896, 225 USPQ at 651 (affirming a holding of obviousness-type double patenting because the claims at issue were obvious over claims in four prior art patents); *In re Berg*, 140 F.3d at 1437, 46 USPQ2d at 1233 (Fed. Cir. 1998) (affirming a holding of obviousness-type double patenting where a patent application claim to a genus is anticipated by a patent claim to a species within that genus).

On appeal, we limit our inquiry to an analysis of whether claim 7 of the '549 patent is invalid for obvious-type double patenting over claim 1 of the '213 patent.7 In accordance with the two-prong obviousness-type double patenting test demarcated in *Georgia-Pacific*, we first construe the claims at issue and determine the differences in subject matter between these two claims. The relevant portion of claim 1 of the '213 patent is directed to a method for treating anxiety in a human by administering an effective amount of fluoxetine or a pharmaceutically-acceptable salt thereof. '213 patent, col. 2, ll. 34-39. Claim 7 of the '549 patent covers a method of blocking the uptake of serotonin by brain neurons in animals by administering the compound fluoxetine hydrochloride. '549 patent, col. 20, ll. 7-9.

[4] A person of ordinary skill in the art would have recognized that fluoxetine hydrochloride is a pharmaceutically-acceptable salt of fluoxetine. In fact, hydrochloride salts are the most common pharmaceutically acceptable salts of basic drugs, and hence are obvious compounds. *See, e.g., The Merck Index of Chemicals and Drugs*(Paul G. Stecher et al. eds., 7th ed. 1960)

(listing multiple hydrochloride salts of drugs).
Therefore, the only difference between claim 1 of the '213 patent and claim 7 of the '549 patent is that the former addresses a method of treating anxiety in humans with fluoxetine hydrochloride while the latter claims a method of using fluoxetine hydrochloride to block serotonin uptake in animals. Having recognized the difference between the claims at issue, we must decide whether this difference renders the claims patentably distinct.

Serotonin uptake inhibition is a natural biological activity that occurs when fluoxetine hydrochloride is administered to an animal, such as a human, for any purpose, including the treatment of anxiety. That is, serotonin uptake inhibition is an inherent property of fluoxetine hydrochloride upon its administration. Barr has offered a panoply of evidence to support the recognition of this inherent biological function of fluoxetine hydrochloride.

In Lilly's March 24, 1998 10-K filing with the Securities and Exchange Commission, Lilly pointed out that serotonin uptake inhibition is the "process by which Prozac works." The title of a 1995 article published by Lilly also indicates that Prozac is a serotonin uptake inhibitor: *Minireview Prozac (Fluoxetine, Lilly 110140), The First Selective Serotonin Uptake Inhibitor and Antidepressant Drug: Twenty Years Since Its First Publication.*8 David T. Wong, Frank P. Bymaster, & Eric A. Engleman, at 1 (1995). The summary of this article "describe[s] the evolutionary process involved in the discovery of the selective 5-HT [serotonin] uptake inhibitor, fluoxetine...." 9 *Id.* at 1. The first full sentence of the article states: "Fluoxetine (Prozac) first appeared in scientific literature as Lilly 110140 (the hydrochloride form), a selective serotonin uptake inhibitor, in the August 15, 1974 issue of *Life Sciences*." *Id.* The article continues: "After twenty-plus years of extensive investigations, inhibition of serotonin uptake remains the major mechanism of action for fluoxetine... ." *Id.*Several tables in the article specifically demarcate amounts of serotonin uptake inhibition resulting from fluoxetine administration. *Id.* at 7, 10-12, 14, 18. The article even illustrates chemical structures of several serotonin uptake inhibitors, one of which is fluoxetine. *Id.* at 9. The article concludes by stating that despite "intensive investigation," including over 5500 research papers on the subject, fluoxetine "is still regarded as a selective [serotonin] uptake inhibitor."

During a deposition, Lilly's expert, Alan Frazer, divulged that "[t]here is no doubt in my mind" that fluoxetine hydrochloride inhibits serotonin reuptake in "the vast majority" of people that ingest fluoxetine hydrochloride. Frazer also stated that he had "no doubt" that inhibition reuptake in brain neurons is the expected consequence of administering fluoxetine hydrochloide. Frazer further acknowledged in a sworn statement that: "Clearly, there are [sic] a wealth of data demonstrating that the uptake of serotonin is inhibited in most humans when fluoxetine is administered."Another one of Lilly's experts, Louis Lemberger, stated in the course of a deposition: "If you give fluoxetine hydrochloride to a human being you are going to inhibit serotonin uptake. . . ." Yet another Lilly expert, Irwin Slater, also agreed that ingesting fluoxetine hydrochloride will result in the inhibition of serotonin uptake in brain neurons.

Likewise, Barr's expert, Fridolin Sulser, stated in an affidavit that "[t]he pharmalogical effect of administering fluoxetine hydrochloride is to inhibit serotonin reuptake in brain neurons." He also recognized that "it is literally impossible to treat someone for anxiety ... with fluoxetine hydrochloride without at the same time inhibiting serotonin reuptake."In an expert report, Dr. Sulser again reiterated that "the primary pharmalogical effect of fluoxetine is the inhibition of serotonin reuptake in brain neurons."He further reiterated that administering fluoxetine hydrochloride "will inherently and inevitably block the reuptake of serotonin... ."He provided a wealth of support for these opinions. Another Barr expert, Robert Roth, also stated that "[t]he biological activity of claim 7 of the '549 patent[] inherently and inevitably occurs whenever someone practices ... the '213 ... patent[]." He continued, stating that "there is no doubt" that "administration of fluoxetine hydrochloride inherently and inevitably blocks the

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reuptake of serotonin... ." Dr. Roth provided a plethora of support for his opinion.

Lilly has not proffered any significant evidence rebutting Barr's ample foundation for the proposition that administration of fluoxetine hydrochloride naturally and inherently inhibits the uptake of serotonin.

A reference is anticipatory if it discloses every limitation of the claimed invention either explicitly or inherently. *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1346, 51 USPQ2d 1943, 1945(Fed. Cir. 1999). A reference includes an inherent characteristic if that characteristic is the "natural result" flowing from the reference's explicitly explicated limitations. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1269, 20 USPQ2d 1746, 1749(Fed. Cir. 1991) (citations omitted). In this case, it is clear from all of the evidence proffered by Barr that the natural result flowing from administration of fluoxetine hydrochloride is inhibition of serotonin uptake. Therefore, the limitation of claim 7 of the '549 patent directed to blocking serotonin uptake by use of fluoxetine hydrochloride is an inherent characteristic of the administration of fluoxetine hydrochloride for any purpose, including the treatment of anxiety.

A patentable distinction does not lie where a later claim is anticipated by an earlier one. That is, a later patent claim that fails to provide novel invention over an earlier claim is not patentably distinct from the earlier claim. Salient aspects of the case at issue are factually similar to *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 32 USPQ2d 1915 (Fed. Cir. 1994). That case involved several patents directed to the use of 3'-azidothymidine ("AZT") to treat individuals infected with the human immunodeficiency virus ("HIV") or individuals who had acquired immunodeficiency syndrome ("AIDS"), and involved United States Patent No. 4,818,750 ("the '750 patent"), which covered a method of using AZT to increase the T-lymphocyte count of persons infected with HIV. *Burroughs Wellcome*, 40 F.3d at 1225, 32 USPQ2d at 1916-17. While never directly addressed by the majority, in his partial dissent, Judge Lourie articulated that the '750 patent should have been invalidated for double patenting because the method claimed in the '750 patent "is an inherent, inevitable result of the practice of the other method patents claiming treatment of HIV or AIDS." *Id.* at 1233, 32 USPQ2d at 1924 (Lourie, J., dissenting-in-part). He stated that because the method claimed in the '750 patent was inherent in the use of AZT to treat HIV and AIDS patients, it lacked novelty. *Id.* He continued, suggesting that allowing a common owner to receive both a patent claiming the physical act of treating individuals that have HIV or AIDS and a patent covering the result that such treatment accomplishes makes "no sense." *Id.* at 1234, 32 USPQ2d at 1924. "It amounts to deciding that treating a person in pain with aspirin is one invention and invoking the pain relieving mechanism by means of that treatment is another." *Id.*

Similarly, in the case at bar, claim 7 of the '549 patent simply describes the process by which fluoxetine hydrochloride physically acts on individuals who receive the drug. That is, fluoxetine hydrochloride inherently blocks serotonin uptake upon administration. Therefore, no patentable distinction rests between administering fluoxetine hydrochloride for treatment of anxiety and inhibition of serotonin uptake by administration of fluoxetine hydrochloride.

The only other difference between claim 1 of the '213 patent and claim 7 of the '549 patent is that the former is directed to humans while the latter is directed to animals. Humans are a species of the animal genus. Our case law firmly establishes that a later genus claim limitation is anticipated by, and therefore not patentably distinct from, an earlier species claim. *In re Berg*, 140 F.3d at 1437, 46 USPQ2d at 1233 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 1053, 29 USPQ2d 2010, 2016(Fed. Cir. 1993); *In re Gosteli*, 872 F.2d 1008, 1010, 10 USPQ2d 1614, 1616(Fed. Cir. 1989); *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782, 227 USPQ 773, 779 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d at 944, 214 USPQ at 767 (C.C.P.A. 1982).

A motion for summary judgment shall be granted "if the pleadings, depositions, answers to interrogatories, and admissions on file, together with affidavits, if any, show that there is no genuine issue as to any material fact, and that the moving party is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(c). A genuine issue of material fact exists if there is sufficient evidence for a jury to return a verdict in favor of the nonmoving party on the particular issue. *Anderson*, 477 U.S. at 248. While the burden rests on the party

moving for summary judgment to show "that there is an absence of evidence to support the non-moving party's case," the nonmoving party must affirmatively demonstrate by specific factual allegations that a genuine issue of material fact exists for trial. *Celotex Corp. v. Catrett*, 477 U.S. 317, 322-23, 325. In this case, Barr moved for summary judgment that claim 7 of the '549 patent was invalid for double patenting over, *inter alia*, claim 1 of the '213 patent. Barr has presented an abundance of evidence indicating that the natural result of fluoxetine hydrochloride is the inhibition of serotonin uptake. Lilly has not proffered sufficient evidence in response to this evidence. Therefore, there remains no genuine issue of fact as to this issue. That is, there is not sufficient evidence on which a jury could base a finding that fluoxetine hydrochloride does not inhibit the uptake of serotonin. Accordingly, the district court erred by indicating that Barr failed to establish that inhibition of serotonin uptake merely describes a biological result of fluoxetine hydrochloride administration for the treatment of anxiety. Further, there is no issue of fact as to whether a human is a species of the animal genus or whether fluoxetine hydrochloride is a pharmaceutically-acceptable salt of fluoxetine. Consequently, the double patenting issue in this case is solely a matter of law.

We have compared the differences between the claims at issue as a whole and conclude that they are not patentably distinct. Therefore, we reverse the district court's denial of the portion of Barr's motion for summary judgment contending that claim 7 of the '549 patent is invalid for obviousness-type double patenting over claim 1 of the '213 patent. Consequently, the portion of Barr's motion for summary judgment pertaining to double patenting is granted. The district court's grant of Lilly's motion for summary judgment pertaining to double patenting is reversed.

IV. CONCLUSION

Because we hold that claim 5 of the '081 patent and claim 7 of the '549 patent comply with the best mode requirement and that claim 7 is invalid for obviousness-type double patenting in view of claim 1 of the '213 patent, we affirm-in-part and reverse-in-part. Further, because we do not reach the issue, we vacate the district court's grant of a jury trial to Barr.

AFFIRMED-IN-PART, REVERSED-IN-PART, AND VACATED.

COSTS

Each party shall bear its own costs.

Footnotes

1 All other issues relating to validity were resolved by consent of the parties. As a result, the district court's judgment disposed of all claims at issue.

2 This section provides, in pertinent part, as follows:

An abbreviated application for a new drug shall contain ...a certification, in the opinion of the applicant and to the best of his knowledge, with respect to each patent which claims the listed drug ... for which the applicant is seeking approval under this subsection ... that such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted. 35 U.S.C. §355(j)(2)(A)(vii)(IV) (1994).

3 This section provides, in pertinent part, that "[i]t shall be an act of infringement to submit ... an application under ... [the Hatch-Waxman Act] ...for a drug claimed in a patent or the use of which is claimed in a patent."35 U.S.C. § 271(e)(2)(A).

4 Application Serial No. 846,448 was a continuation-in-part of Serial No. 544,654 (October 24, 1983), which was a continuation of Serial No. 872,147 (January 25, 1978), which in turn was a divisional of Serial No. 432,379 (January 10, 1974).

5 A patent owner cannot avoid double patenting by disclaiming the earlier patent. Further, because Lilly disclaimed the '213 patent, it cannot now terminally disclaim the '549 patent to expire at the time the '213 patent would have expired had it not been disclaimed. That is, the fact that the '213 patent has been disclaimed is of no help to Lilly, as double patenting precludes claim 7 of the '549 patent from extending beyond the termination date of the '213 patent, whether that termination date is at the end of its normal term or, as in this case, is the date it is terminated via disclaimer.

6 An absence of overlap between the later claim and the earlier claim does not preclude a conclusion that the later claim is patentably indistinct from the earlier claim.

7 A two-way double patenting test does not apply in this case. The two-way test is only appropriate in the unusual circumstance where, *inter alia*, the United States Patent and Trademark Office ("PTO") is "*solely* responsible for the delay in causing the second-filed application to issue prior to the first." (emphasis added). *In re Berg*, 140 F.3d at 1437, 46 USPQ2d at 1233 (Fed. Cir. 1998); *see also In re Goodman*, 11 F.3d 1046, 1053, 29 USPQ2d 2010, 2016(Fed. Cir. 1993) (holding that PTO actions did not dictate the rate of prosecution when Goodman accepted early issuance of species claims and filed a continuation application to prosecute genus claims). Such circumstances are not present in this case, because the PTO was not solely responsible for the delay. Indeed, the '549 patent issued in December 1986, approximately eight months after a continuation-in-part was filed, which stemmed from a continuation application , which in turn stemmed from a divisional of the original '379 application that was filed in January 1974. Further, an expert hired on behalf of Lilly in the matters of PTO and corporate intellectual property practice, in discussing claim 7 of the '549 patent, stated: "[I]t is true that the claim could have been presented earlier... ." This statement indicates that the delay was not solely caused by the PTO.

8 The reference to "selective" means that fluoxetine hydrochloride inhibits the uptake of serotonin to a greater degree than it inhibits the uptake of other monoamines (such as dopamine or norepinephrine).

9 The Wong article defines 5-HT as serotonin. Wong at 2.

- End of Case -

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